REMARKS

Applicants have amended their specification to correct errors therein, including typographical errors. It is respectfully submitted that these amendments to the specification do not add new matter to the application.

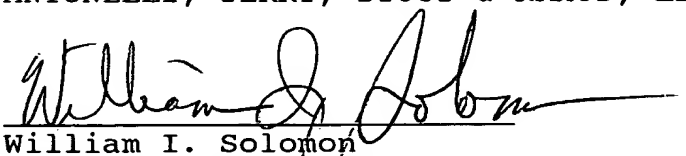
Entry of the present amendments, and examination of the above-identified application in due course, are respectfully requested.

Attached hereto is a marked-up version of the changes made in the specification by the current Amendment. This marked-up version is on the attached pages, the first page of which is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE".

To the extent necessary, Applicants petition for an extension of time under 37 CFR § 1.136. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to the Deposit Account No. 01-2135 (Case No. 506.40278X00) and please credit any excess fees to such Deposit Account.

Respectfully submitted,

ANTONELLI, TERRY, STOUT & KRAUS, LLP



William I. Solomon
Registration No. 28,565

1300 North Seventeenth Street
Suite 1800
Arlington, VA 22209
Tel.: 703-312-6600
Fax.: 703-312-6666

WIS/slk

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

Please delete the paragraph at page 2, lines 4-23, and substitute therefor the following new paragraph:

It is known that the pH of interstitium is lowered to a level of 6.9 in cancer cells etc. and that administration of glucose lowers the pH of interstitium from 6.9 to 6.2 [H. Kahler and W.V. Robertson, J. Natl. Cancer Inst., 3, 495 (1943), P.M. Gullino et al., J. Natl. Cancer Inst., 34, 857 (1965)]. It is also known that inflamed parts have a pH in the acidic range, i.e. pH 6.5 [V. Menkin, Biochemical Mechanism in Inflammation, Thomas, Springfield, III, pp. [69-7] 69-77 (1956)]. Further, it has been experimentally demonstrated that transient ischemia in rats lowers the pH of the affected part from 7.4 to 6.5 [N. Watanabe et al., Biochem. Pharmacol., 38, 3477 (1989)]. Also known is a pH-sensitive drug delivery system (DDS) for superoxide dismutase (SOD) using a styrene-maleic acid copolymer (SM) [Biochemistry, 28, 6619 (1989), Biochem. Pharmacol., 38, 3477 (1989)]. In this DDS, superoxide dismutase covalently binds to the styrene-maleic acid copolymer (SM-SOD) noncovalently binds to the warfarin site on albumin in blood at pH around neutrality. As the pH is lowered, SM is protonated and the albumin-binding ability thereof is decreased to cause release of SM-SOD.

Please delete the paragraph from page 3, line 31 to page 5, line 4, and substitute the following new paragraph:

There is no specific restriction as to the compounds having a free amino group to be used in the present invention. Suitable compound include pharmaceutical compounds, for example, peptides, proteins and enzymes such as bradykinin, angiotensin, anthriopeptin, oxytocin, vasopressin, adrenocorticotropin (ACTH), calcitonin, insulin, glucagon, cholecystokinin, β-endorphin, melanocyte-inhibiting factor, melanocyte-stimulating hormone, gastrin antagonist, neurotensin, somatostatin, brucine, cyclosporin, enkephalin, transferrin, RGD peptide, thyroid hormone, growth hormone, gonadotropic hormone, luteinizing hormone (LHRH), asparaginase, arginase, uricase, carboxypeptidase, glutaminase, SOD, tissue plasminogen activator (t-PA), streptokinase, interleukin, interferon, muramyl dipeptide, thymopoietin, granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), erythropoietin (EPO), thrombopoietin (TPO), trypsin inhibitor, lysozyme, EGF, insulin-like growth factor (IGF), nerve growth factor (NGF), platelet-derived growth factor (PDGF), transforming growth factor (TGF), endothelial cell growth factor (ECGF), fibroblast growth factor (FGF), glia cell growth factor (GGF), thymosin and specific antibodies (e.g., anti-EGF receptor antibody); carcinostatic agents such as doxorubicin derivatives [e.g., 3'-(D-Val-Leu-Lys)-[doxorubisin] <u>doxorubicin</u>], 5-fluorouracil derivatives [e.g.,

L-Ala-2-(5-fluorouracil-1-yl)-Gly], daunorubicin, idarubicin and neocarzinostatin; amino acid derivatives such as dopamine; amoxicillin, ampicillin, amantadine hydrochloride, epirubicin hydrochloride, doxorubicin hydrochloride, dopamine hydrochloride, vancomycin hydrochloride, talampicillin hydrochloride, bacampicillin hydrochloride, cycloserine, ciclacillin, cefaclor, cefatrizine, cefadroxil, cefalexin, [cefaradine] cefradine, [cefaloxazine] cefroxadine, tranexamic acid, norepinephrine, methyldopa, melphalan, liothyronine sodium, astromicin sulfate, isepamicin sulfate, kanamycin sulfate, [cyclonomycin] micronomicin sulfate, sisomicin sulfate, dibekacin sulfate, [sulbekacin] arbekacin sulfate, neomycin sulfate, netilmicin sulfate, paromomycin sulfate, bleomycin sulfate, levodopa, and antibody drugs [e.g., human serum immunoglobulins (e.g., pepsin-treated human serum immunoglobulin, plasmin-treated human serum immunoglobulin, β-propiolactone-treated human serum immunoglobulin, S-alkylated human serum immunoglobulin, S-sulfonated human serum immunoglobulin and polyethylene glycol-treated human serum immunoglobulin), mouse monoclonal antibodies, human monoclonal antibodies, chimera antibodies, anti-idiotype antibodies and Fab fragments comprising variable region only].

Please delete the paragraph from page 8, line 31, to page 9, line 14, and substitute therefor the following new paragraph:

Bovine pancreatic insulin (0.2 mg, Wako Pure Chemical

Industries, Ltd.) was dissolved in 1 mL of a 1 mmol/L aqueous solution of hydrochloric acid. To about 25 mg of sialyllactose of 75% purity (a mixture of 3'-sialyllactose and 6'-sialyllactose, Boehringer Mannheim GmbH) was added 0.1 mL of a 600 mmol/L aqueous solution of disodium [phosphate] hydrogenphosphate to make a solution. The insulin solution (0.1 mL) and the sialyllactose solution (0.1 mL) were mixed in a test tube to give a mixture having a pH of about 7.8. The test tube was put into a constant temperature water bath at 40°C to cause reaction and left for 3 days. The reaction mixture was sampled inttermittently, followed by centrifugation at 3000 rpm for 20 minutes to remove insoluble materials. The samples collected 0, 1 and 3 days after the start of the reaction were analyzed for products obtained by the reaction of insulin with sialyllactose by HPLC under the following conditions.